5. STUDY RECORD MAINTENANCE

One of the primary responsibilities of the Westat CRA during a site visit is to review the study records and ensure that they are complete and accurate. This chapter describes the different types of study records and what the Westat CRA will review during a site visit.

5.1 Regulatory Binder

The Regulatory Binder contains all study-specific information and regulatory documentation. The binder does not include completed CRFs or signed informed consent forms. The terms Study Binder, Investigator Binder, Administrative Binder, Regulatory Files, and Investigator's Study Files are used synonymously to describe the Regulatory Binder. The Regulatory Binder may take the form of file folders, one or more three-ring binders, a filing system, or a combination of these organizational methods. The site keeps all original informed consents that have been signed by participants. It is recommended these be maintained in a separate binder.

Typically the Regulatory Binder contains the elements described in the Regulatory Binder checklist. The order and organization of the documents may vary from site to site. During a site visit, the CRA will expect to review the Regulatory Binder to ensure its completeness.

5.1.1 Regulatory Binder Checklist

The following documents should be found in the Regulatory Binder, though the order may vary by site:

- Protocol and amendments (all versions).
- Investigator brochure (all versions).
- CRFs (blank set that can be duplicated, all versions).
- Form FDA 1572s (all versions).

- Curricula vitae (CV) and documentation of professional licensure of all investigators (from time of study initiation to date).
- Human subject protection training documentation (from time of study initiation to date).
- Financial disclosure forms for anyone listed on the 1572, if applicable.
- IRB approval documentation for:
  - The protocol (all versions);
  - Protocol amendments (all versions);
  - Informed consent form document (original and all versions);
  - Other written (educational) materials provided to the participants;
  - Continuation of the study (based on annual or periodic reviews); and
  - Study advertising.
- IRB correspondence
  - Notification of new safety information and the IRB's recommendations pertaining to this information.
  - IRB roster and credentials of IRB members.
- NCI-DCP approval documentation for:
  - The protocol (all versions);
  - Protocol amendments (all versions);
  - Informed consent form document (original and all versions);
  - Other written (educational) materials provided to the participants; and
  - Pertinent recruitment and retention materials.
- NCI-DCP correspondence
- Informed consent
  - Original copies of IRB-approved versions and
  - Original copies of NCI –approved versions.

NOTE: Original, signed informed consents are usually kept in the participant's medical records or research records and not in the Regulatory Binder.

- SAEs and IND safety reports.
- Signature and delegation log (site personnel signature sheet).

  NOTE: This is a comprehensive list of all research staff involved in the conduct of the study. The log includes signatures, initials, delegated tasks, and effective dates.

- Site monitoring log.
- Site visit reports and confirmation letter.
- Participant screening log/registration log.

  NOTE: This documents the chronological screening/enrollment of participants. This log is kept under lock and key separate from the Regulatory Binder.

- Clinical laboratory certification (if required) and normal ranges (from time of study initiation to date).
- Study agent documentation

  - Agent shipment and receipt records/forms;
  - Accountability logs; and
  - NCI DARFs.

  NOTE: Study agent documentation may be kept in the pharmacy, and not in the Regulatory Binder.

- Study closeout information.

5.2 Source Documentation

Source documents are the original records of participant information (e.g., the medical record) and contain all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator is required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record

(including data recorded on Case Report Forms) must originate in the participant's medical record or study record.

5.2.1 List of Source Documents

Source documents, which may be either paper or electronic, may include but are not limited to the following items.

- Institutional, research, clinic, or office records containing:
  - Inpatient and outpatient medical records;
  - Progress notes;
  - Consults;
  - Nursing notes;
  - Pathology reports;
  - Radiology reports;
  - Medicine/radiation administration records;
  - Surgical reports;
  - Laboratory results;
  - Admission forms;
  - Flow sheets and study-specific checklists that are signed and dated;
  - Discharge summaries;
  - Protocol or study road maps;
  - Appointment books; and
  - Participant diaries/calendars.
- Relevant participant-specific written communication from nonstudy health care providers, including comments related to past medical history, entry criteria, or other referral or followup information;

- Participant-specific correspondence, such as documented telephone calls, email messages, and faxes; and
- Obituaries, autopsy reports, and death certificates.

5.2.2 Source Documentation Guidelines

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Participant's initials, year of birth, or study identification number included on each page.
- Legibly written in ink or clearly labeled.
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant.
- Correction liquid or tape must not be used in source documents or on CRFs. Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

5.3 Case Report Forms

Participant information that relates to a clinical study is transferred from the source documents to CRFs. The PI or designee for each DCP study typically develops the CRFs for use in a particular study. However, DCP does provide sample CRF templates for use with phases I and II DCP chemoprevention trials. These templates contain recommended content and formats and may be downloaded (http://www3.cancer.gov/prevention/pio/crf-forms.pdf) and modified with study-specific information for each trial.

NOTE: Section C2 "Subject Enrollment Form" has a subsection C2.3 "Race." The race criteria were updated January 2002. All studies approved after January 2002 should use the new criteria, which can be found in the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (as amended October 2001), in Section IV Definitions, letter E. Racial and Ethnic Categories. This policy can be found at the following web site: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

NOTE: In most cases, CRFs consist of single or triplicate paper forms that an authorized person completes by hand by transferring data from the source documents. Increasingly, however, sites may have the authorized staff person transfer data directly from the source into an electronic database, essentially creating an electronic CRF. These electronic records may be printed and filed in the participants' CRF notebook for monitoring purposes or any alternative mechanism may be used that allows appropriate access to electronic CRF information for monitoring purposes.

The Westat CRA will review participant CRFs to ensure that they are being filled out or entered properly. The CRA will verify that all data entered on the CRFs can be validated by information in the source documents. The CRA will also review the source documents to ensure that the pertinent information is included on the CRFs.

5.3.1 Completing a CRF

- Any assigned member of the study staff who has signed the Signature Log in the Regulatory Binder may complete a CRF.
- CRFs should be completed within 1 week after the relevant information becomes available (i.e., the participant completes the visit or the laboratory results have been received).
- The information documented on the CRF **must be identical** to the information found in the source document (i.e., participant charts, laboratory result printouts).

  NOTE: All source documents and CRFs must be available for verification by the Westat Team CRA during site monitoring visits.
- If the source information is **missing**, write or enter "ND" (no data) in the boxes/space. If the information is **unknown**, write or enter "UNK" in the boxes/space. Entries of "Missing" or "Unknown" information must be explained in the source document (i.e., nurse's or clinic notes) for future verification.

- Enter information on a paper CRF with an ink (preferably black) pen only. Do not use pencil.

- When boxes are provided for a response and CRFs are completed by hand, be sure to clearly mark the box to be selected with a ✓ or —. Make sure the mark is clear.

- For CRFs filled out by hand, make corrections in ink by crossing out the incorrect entry with a single horizontal line, placing the correct information next to the error, and providing an initial and date next to the correction. Do not backdate. Do not use any type of correction fluid or erase any entries on the forms.

  NOTE: Corrections to electronically-created CRFs must be made within the same database that was used to create them—that is, not simply crossed out on the paper printout. If the site uses an electronic system to create CRFs, then it should also have in place a method to track data edits, including who made them, and when.

- Do not write in the margins of the CRFs. Provide any relevant additional information in the appropriate "comments" section.

- Avoid the use of abbreviations other than those that have been recommended.

- CRFs are required for the following participants:

  - All participants who received a procedure required by protocol after signing informed consent and

  - All participants who have been randomized.

  NOTE: CRFs are not required for potential study participants found to be ineligible for study enrollment.

5.4 CRF Notebook

CRFs contain participant information related only to the study. Each participant has a CRF notebook or folder, or another system is used to organize the participant's CRFs. Hard-copy and/or electronic CRFs should be kept in a locked and secure area at all times.

The CRF notebook is arranged in a protocol-specific logical order. The forms in each section may be arranged chronologically or in reverse chronological order. In either case, there must be consistency throughout the notebook.

Each CRF should be identified by PID, study visit, and visit date. Each notebook or folder should be organized into the following sections (as appropriate):

1. Demographic information;
2. Pretreatment section;
    - Eligibility checklist;
    - Registration/randomization forms;
    - Confirmation of registration;
    - On study form; and
    - All other required forms to be completed and/or submitted prior to treatment.
3. Intervention section (arranged by cycle, study week, or other time point)
    - Procedure forms and/or flow sheet;
    - Concomitant medications;
    - AE and SAE reports; and
    - Lab data.
4. Tumor evaluation/response to intervention (if applicable)
    - Radiology forms;
    - Cytology report;
    - Pathology results; and
    - Bone marrow aspiration results.
5. SAEs (as needed)
    - Copy of supporting and followup documentation.
6. Off study
    - Off study forms.
7. Followup Forms
    - Death report form;

- Late AEs documentation; and
- Correspondence relating to participant status (relapse, additional treatment, etc.).

5.5 Record Retention

The U.S. Department of Health and Human Services (DHHS) and the FDA have regulations related to retention of protocol records.

- The Department of Health and Human Services Regulations (45 CFR 46.115) apply for all research conducted or supported by any Federal department or agency. This regulation states that IRB records relating to research conducted shall be retained for at least 3 years after completion of the research. The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research.
- Trials with a FDA IND must additionally comply with 21 CFR 312.57 and 21 CFR 312.62. These regulations apply to investigational agent records, investigator financial interest records, and patient case histories. Both of these regulations require that the sponsor retain records and reports for 2 years after a marketing application is approved for the agent. If an application is not approved for the agent, the sponsor retains records and reports until 2 years after shipment and delivery of the agent for investigational use is discontinued and FDA has been so notified.
- The contract awarded for each study indicates how long records are retained for that study. This information is specified in the study protocol.